REMARKS

Any fees that may be due in connection with filing this paper, or with this application during its pendency, may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition.

35 U.S.C. § 103

The Examiner alleges that claims 24, 25, 27-39 and 40-45 are obvious over Oka *et al.* (*Sankyo Seimei Kagaku Kenkyu Shinko Zaidan Kenkyu Hokokushu* 12:46-56 (1998); "Oka"), in view of Reff and Heard (*Critical Reviews in Oncology and Hematology* 40:25-35 (2001); "Reff"). Applicants note that the rejection of claim 39 is moot, as that claim was cancelled in the previous response filed December 6, 2007.

According to the Examiner, Oka allegedly teaches an immunotoxin containing: (1) a full length 2D7 antibody that binds to an HLA Class I antigen, and (2) a recombinant α-sarcin. The Examiner states that, while Oka admittedly does not teach or suggest modifying the 2D7 antibody to produce a minibody, Reff allegedly cures this deficiency by teaching that the generation of minibodies from whole antibodies increases their efficacy in oncology applications by decreasing their half-life in circulation and increasing their ability to penetrate solid tumors.

The Examiner further states that one of ordinary skill in the art would have been motivated to produce a minibody as taught by Reff from the antibody taught by Oka because the minibody "would have increased cytotoxic activity because it is better able to penetrate tumors." She alleges that one would have a reasonable expectation of success in doing so because (1) Oka teaches that the 2D7 antibody (by itself, without conjugation to a toxin) has no cytotoxicity; (2) Reff teaches that a minibody has a shorter half-life in circulation and increased penetration of tumors; and (3) therefore, a minibody of 2D7 necessarily would have higher cytotoxicity than the whole antibody. The Examiner concludes that there is a *prima facie* case of obviousness.

This rejection is traversed.

Analysis

In order to set forth a *prima facie* case of obviousness under 35 U.S.C. § 103(a), there must be some teaching, suggestion or incentive supporting the combination of the cited references to produce the claimed invention (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F.2d 1572, 1577, 221 USPQ 329, 933 (Fed. Cir. 1984)); (2) the combination of the cited references must actually teach or suggest the claimed invention; and (3) those of skill in the art must have had an expectation of success upon producing the claimed invention. These standing principles of U.S. law regarding obviousness were essentially unaltered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S. Ct. 1727 (2007). The Court in KSR took the opportunity to reiterate that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit some reason that would have led a person having ordinary skill in the art to modify a known composition in a particular manner and thereby result in the claimed compositions. Absent such a reason, the claimed composition would not be obvious. The Court further noted that when there is a "design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions," it would be obvious to try those predictable solutions, and if they produced the expected success, the success could not be considered to be innovative.

The pending claims are directed to:

(1) methods of producing an HLA class I antigen-recognizing minibody by (a) *identifying a whole antibody that recognizes an HLA class I antigen*; (b) producing a minibody version of the antibody of (a); and (c) assaying a cytotoxic activity of the minibody (Claim 24 and dependents); and

(2) methods of producing a minibody *whose CDRs are derived from the CDRs of an HLA class I antigen-recognizing whole antibody*, where the minibody has a level of cytotoxic activity greater than that of the whole antibody and the method includes (a) providing a DNA encoding the minibody; (b) expressing the minibody from the DNA; and (c) confirming that the expressed minibody possesses cytotoxic activity greater than that of the whole antibody (Claim 35 and dependents).

Oka teaches that an immunotoxin conjugate made up of a full length 2D7 antibody and recombinant α–sarcin (a toxin) is cytotoxic against myeloma cells. Oka teaches that the 2D7 antibody portion of the immunotoxin targets the conjugate to the myeloma cell, where the toxin exerts its cytotoxic effects. Oka further teaches that in the absence of the toxin, the 2D7 antibody alone exhibits no cytotoxicity against myeloma cells. As the Examiner has acknowledged, Oka does not teach or suggest producing a minibody of any sort, from 2D7 or any other antibody.

Reff is cited for its teaching that making an antibody smaller can (a) decrease its half-life in circulation (pages 30-31) and (b) permit it to penetrate solid tumors more easily (page 31, first full paragraph). The Examiner does not explain why either of these potential consequences could incentivize someone to produce a minibody version of Oka's 2D7 antibody in particular (whether conjugated to α–sarcin toxin or not), much less to carry out all of the steps of the presently claimed methods.

First, Oka makes it clear that the full-length 2D7 antibody itself is not cytotoxic to myeloma cells in culture. There is no reason whatsoever to expect that a minibody version of 2D7 would somehow acquire a cytotoxic activity not possessed by full-length 2D7. The Examiner appears to believe that, since making an antibody smaller can allow it to penetrate solid tumors more easily (see Reff at page 31, first full paragraph), that somehow equates with increased cytotoxic activity. Applicants point out that merely reaching and even binding to cells in the tumor does not necessarily correlate with cytotoxic activity. An antibody must do something more than simply bind to a cell-surface antigen in order to be cytotoxic. See, for example, Oka's teachings regarding the lack of toxicity of 2D7 in cultured RPMI 8226 cells, where "penetration" by the antibody is not a factor.

Second, Reff's statement about smaller size and penetration of solid tumors is irrelevant to the present case, as Oka's teachings concerned an antibody that binds to myeloma cells—in particular, myeloma cells in culture and those obtained from the blood of myeloma patients.

Solid tumors were not addressed by Oka. Thus, there would be no reason to seek a smaller version of 2D7 merely so that it could potentially penetrate solid tumors more readily.

Third, one of ordinary skill would understand from Oka that the protein synthesis-inhibiting effect of Oka's conjugated immunotoxin was derived from the α-sarcin part of the conjugate, and not from the 2D7 part. Nothing in either cited reference would induce one of ordinary skill to imagine that 2D7, nor a minibody produced from 2D7, would exhibit any cytotoxic activity if it were not attached to a toxin. Thus, one of ordinary skill in the art would have no reason to conclude, as does the Examiner, that "the minibody of Reff and Heard would have increased cytotoxic activity either with or without the fusion of the toxin" (Office action at page 5). According to Oka, the presence of the toxin was essential to the cytotoxic activity of 2D7.

Fourth, the Examiner's assumption (Office action pages 4-5, carryover paragraph) that decreasing the half-life of an antibody in circulation is an advantage that would increase the antibody's efficacy in oncology applications is not warranted. In fact, Reff says the opposite. Reff generally teaches that a modification that decreases half-life in circulation makes the antibody less efficacious: "However, many of the antibody constructs designed to increase cytotoxicity have a much shorter half-life, making them less efficacious." (Reff at page 30, second column, third full paragraph; emphasis added.) Reff does go on to say in the same paragraph that there are situations in which a shorter half life may be desirable, naming radioactive antibody fragments as an example. This is because a long half-life in circulation would expose healthy tissue to radiation: see Reff at page 31, first column, third full paragraph. It seems clear from Reff that a conjugate of a toxin and an antibody would not generally be a situation in which decreased half-life would improve efficacy. And this only makes sense: the longer the conjugate is present in the body, the more will be bound by the target cells. Thus, rather than provide a motivation to make a minibody version of Oka's 2D7/toxin conjugate, Reff's teachings about decreased half-life of smaller antibody fragments actually *teaches away* from doing so.

Fifth, Applicants remind the Examiner that the claims are drawn to methods. Independent claim 24 requires a step of assaying a cytotoxic activity of a minibody (not an immunotoxin). Since Oka teaches that full-length 2D7 has no cytotoxic activity, there would have been no reason to expect that a minibody version of 2D7 would have cytotoxic activity, and thus no reason to assay for such activity. *A priori* there would have been no reason to determine whether the minibody has an increased cytotoxic activity compared to the whole antibody, as required by dependent claim 25, and no reason to expect one could in fact confirm that it does so, as required by independent claim 35.

In summary, Applicants submit that one of ordinary skill in the art would have neither the motivation to carry out the claimed methods in order to produce and test a minibody version of Oka's 2D7 antibody, nor a reasonable expectation of success upon doing so. One of the motivations cited by the Examiner, i.e., the increased penetration of solid tumors by smaller antibody fragments, is not relevant to Oka's myeloma-binding 2D7 antibody. The other cited motivation, i.e., the decreased half-life of the fragments, is actually a *teaching-away*, not a motivation. Further, there is no reason to expect that a minibody version of 2D7 would possess any cytotoxic activity at all, since Oka shows that the full-length 2D7 does not. Accordingly, the art provides no reason to carry out the assay required by claim 25 or the confirmation step required by claim 35, and certainly no expectation of success upon doing so. Applicants' results were entirely unexpected in view of the art.

Applicants submit that the Office has not established a *prima facie* case of obviousness against claims 24, 25, 27-38, and 40-45 based on the combination of Oka and Reff, and has not given proper weight to Applicants' unexpected results. Withdrawal of the obviousness rejection of claims 24, 25, 27-38, and 40-45, and allowance of the claims, is therefore requested.

Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

Respectfully submitted,

Date: August 5, 2008

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
Customer No. 26161
Telephone: (617) 542-5070
Facsimile: (877) 769-7945